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Chromogranin A: A Valuable Serum Diagnostic Marker for Non-Insulinoma Neuroendocrine Tumors of the Pancreas in a Chinese Population

Authors' Contribution:
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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Pancreatic neuroendocrine tumors (P-NETs) are uncommon neoplasms, with few studies to date assessing serum biomarkers for the diagnosis of P-NETs. This study assessed the ability of serum chromogranin A (CgA) concentrations to distinguish P-NETs from other pancreatic lesions in a Chinese population and to determine the histological grades of P-NETs.

Material/Methods: This prospective study enrolled 165 patients, including 73 with proven P-NETs, 60 with malignant tumors of the pancreas, and 32 with benign lesions of the pancreas. Serum CgA concentrations were measured by ELISA.

Results: Serum CgA concentrations were significantly higher in patients with P-NET than in patients with other pancreatic malignancies and benign lesions (P<0.001), but did not differ significantly in the latter 2 groups (P=0.827). Serum CgA concentrations were significantly higher in patients with non-insulinoma P-NETs than in the other groups (P<0.001), but did not differ significantly in patients with insulinoma and patients with non-P-NETs (P=0.668). Receiver operating characteristic (ROC) curves revealed that a serum CgA concentration of 77.8 ng/ml could distinguish patients with non-insulinoma P-NETs from patients with non-P-NETs, with a sensitivity of 96.7%, a specificity of 76.1%, and an area under the ROC curve of 0.897. In patients with P-NETs, multifactor analysis showed that the non-insulinoma subtype and the presence of liver metastases were associated with elevated serum CgA (both p<0.001).

Conclusions: Serum CgA concentration may be a valuable diagnostic biomarker for non-insulinoma P-NETs. Elevated serum CgA is likely associated with liver metastases.

MeSH Keywords: Biological Markers • Chromogranin A • Insulinoma • Neuroendocrine Tumors

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Background

Pancreatic neuroendocrine tumors (P-NETs) are rare pancreatic neoplasms arising from neoplastic neuroendocrine cells that retain the pleuri-hormonal capabilities of dedifferentiated progenitor cells [1–3]. Most P-NETs are sporadic, although some are associated with hereditary cancer syndromes, including multiple endocrine neoplasia type 1 (MEN1) and von Hippel-Lindau disease (VHL). Although studies from Europe and Asia have reported that P-NET has an annual incidence of <1/100 000 [4–10], autopsy series have reported a prevalence rate of 10%, suggesting that the incidence of P-NET was underestimated [11,12]. Moreover, studies have shown that the prevalence and incidence of P-NET have been increasing for decades [13–17].

Clinically, P-NETs can be classified as functional and non-functional tumors, depending on the occurrence of hormone secretion symptoms. Functional P-NETs include insulinomas, glucagonomas, gastrinomas, vasoactive intestinal peptideomas (VIPomas), and pancreatic polypeptide-producing tumors, all of which are characterized by hormone overexpression. Non-functional P-NETs give rise to nonspecific clinical symptoms, which may delay diagnosis. The overall prognosis and long-term survival are far better for patients with P-NET than for patients with exocrine pancreatic cancer [18,19]. Earlier diagnosis of P-NET can facilitate radical surgical resection and enhance long-term prognosis. The identification of serum biomarkers diagnostic for P-NETs may improve long-term prognosis of these patients.

Chromogranin A (CgA), the first member of the chromogranin/secretogranin family to be identified, is a 460 amino-acid protein with a molecular mass of 70 to 85 kDa. CgA mRNA and protein are expressed throughout the neuroendocrine system, including in all types of neurons, and elevated expression of CgA may be diagnostic of NETs [20]. Serum CgA concentration was shown to be a reliable diagnostic biomarker for gastroenteropancreatic NETs (GEP-NETs), as well as being useful for evaluating tumor status and responses to treatment [21–28]. Consensus guidelines in western countries have recommended that CgA be measured routinely for the diagnosis and surveillance of GEP-NETs [29–31].

The relationships between CgA concentrations and non-insulinoma subtypes have also been investigated. For example, elevated CgA has shown high sensitivity in diagnosing gastrinomas, glucagonomas, and non-functioning NETs [32,33]. At present, however, serum CgA concentrations are not routinely used for the clinical assessment of patients diagnosed with GEP-NETs in China. Moreover, few studies have assessed the ability of CgA to diagnose P-NETs. The present study therefore investigated the role of serum CgA in the differential diagnosis of P-NETs from other pancreatic lesions, and its diagnostic value in different subtypes and histological grades of P-NETs.

Material and Methods

Patient enrollment

Patients with pancreatic lesions detected by enhanced computed tomography (CT), magnetic resonance imaging (MRI) with contrast, or endoscopic ultrasound (US) at Shanghai Ruijin hospital were enrolled prospectively from March 2015 to June 2019. Patients were included if they were aged 16 to 75 years and if immunohistochemical diagnostic data were available for lesion tissue samples obtained surgically or by biopsy at Shanghai Ruijin hospital. Patients were excluded if they had taken a proton pump inhibitor (PPI) or a somatostatin analogue within 2 weeks before collection of blood samples. Patients were also excluded if they had been diagnosed with serious comorbidities, including cardiovascular disease (e.g., arterial hypertension, cardiac insufficiency, acute coronary syndrome), renal insufficiency, hepatic disorder, or inflammatory bowel disease; or if other malignancies were present. The study protocol was approved by the ethics committee of Shanghai Ruijin hospital, and all patients provided written informed consent.

Serum CgA determination

Before surgery or biopsy, fasting blood samples were collected; and sera were obtained by centrifugation and stored at -80°C. Serum CgA concentrations were measured by ELISA (Chromoa assay; CIS Bio International), according to the manufacturer's instructions. Figure 1 shows the study protocol.

Statistical analysis

Continuous data were reported as means with ranges, and inter-group differences in CgA concentrations were analyzed by the Mann-Whitney U test or the Kruskal-Wallis test, as appropriate. Receiver operating characteristic (ROC) curves were plotted and the area under the curve (AUC) was calculated to determine the diagnostic value of serum CgA. The χ^2 test or Fisher's exact test was utilized in univariate analyses of the relationships between clinical features and serum CgA concentrations. Factors significant in univariate analysis were entered into a multivariate logistic regression model to identify factors independently associated with CgA concentrations. All statistical analyses were performed using SPSS version 22.0, with a P value <0.05 considered statistically significant.

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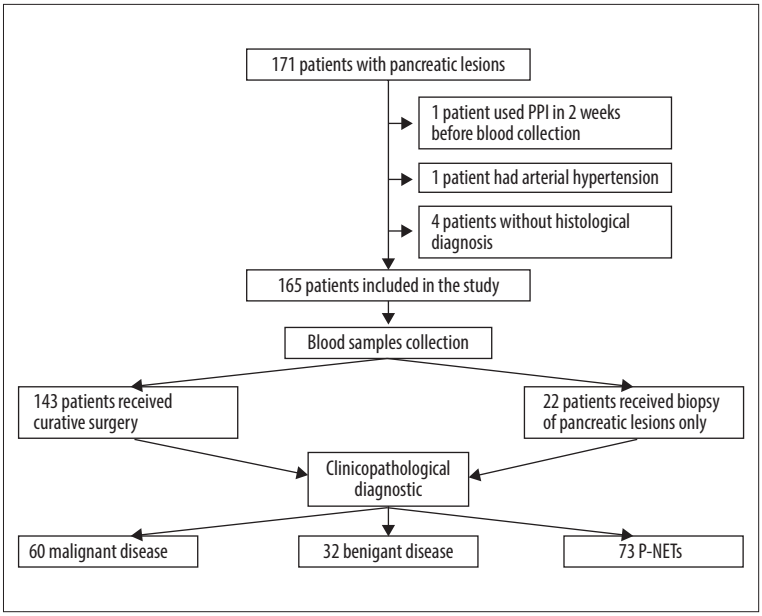

Figure 1. Flow-chart of the patient population.

Results

Patients' demographic and clinical features

Of the 171 patients with pancreatic lesions, 165 were included in this study (Figure 2). Six patients were excluded, including 4 who were not diagnosed histologically, 1 who had taken a PPI within 2 weeks before blood sample collection, and 1 with arterial hypertension. Of the 165 patients included in the study, 73 were diagnosed with P-NETs, including 43 with insulinomas, 1 with a gastrinoma and 29 with non-functional P-NETs; and 92 were diagnosed with other pancreatic lesions, including pancreatic adenocarcinomas, intraductal papillary mucinous neoplasms, and serous cystadenomas.

Table 1 shows the demographic and pathological characteristics of the 73 patients with P-NETs. Of these patients, 61 underwent curative surgery, whereas 12 were biopsied to confirm the pathological characteristics of their pancreatic lesions. Table 2 shows the demographic and clinicopathological characteristics of the 92 patients with non-P-NETs, including 60 with malignant and 32 with benign pancreatic lesions. Of these 92 patients, 82 underwent surgical resection.

Diagnostic value of serum CgA in patients with pancreatic lesions

Figure 2 shows the serum CgA concentrations in the P-NET and non-P-NET groups. Median serum CgA concentration was significantly higher in the P-NET (92.27 ng/ml; range: 61.73–492.77 ng/ml) than in the non-P-NET (68.32 ng/ml, range: 20.79–247.85 ng/ml) group (P<0.001). Subgroup analysis of patients in the non-P-NET group showed that median

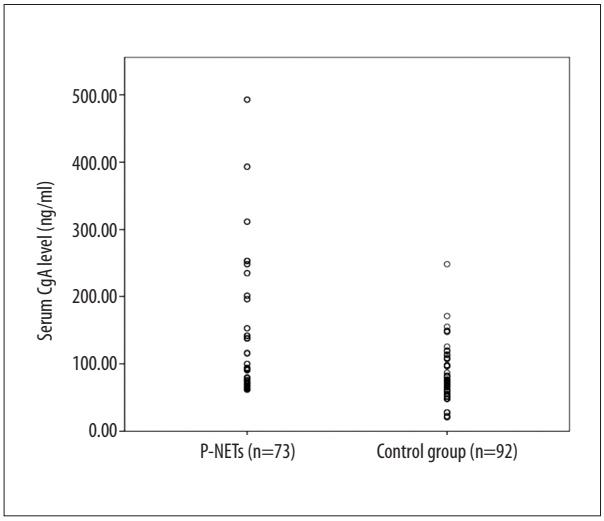

Figure 2. Serum CgA concentrations of patients in the P-NET and non-P-NET groups.

CgA levels did not differ significantly between patients with malignant (68.32 ng/ml, range: 48.24–247.85 ng/ml) and benign (69.16 ng/ml, range: 20.79–148.95 ng/ml) pancreatic lesions (P=0.827; Figure 3). In contrast, subgroup analysis of patients in the P-NET group showed that median serum CgA levels were significantly higher in patients with non-insulinomas (139.87 ng/ml, range 75.74–492.77 ng/ml) than in patients with insulinomas (70.29 ng/ml, range: 61.73–252.73 ng/ml) (P=0.001). CgA concentrations did not differ significantly between patients with insulinoma and patients with non-P-NETs (P=0.668), but were significantly higher in patients with non-insulinomas than in patients with non-P-NETs (P<0.001) (Figure 3).

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Table 1. Demographic and pathological characteristics of patients with P-NETs.

Demographic and pathological features		Number n=73	
Gender	Male	29	(39.7%)
Age (years) at diagnosis	Median (range)	49	(16-75)
P-NENs subtype	Insulinoma	43	(58.9%)
	Non-insulinoma P-NENs	30	(41.1%)
	NF*	29	
	Gastrinoma	1	
Surgery or not	Curative surgery	61	(83.6%)
	Non-resection	12	(16.4%)
Liver metastasis or not	No	61	(83.6%)
	Yes	12	(16.4%)
Grade	G1	45	(61.6%)
	G2	20	(27.4%)
	G3	8	(11.0%)
Stage	I	45	(61.6%)
	II	16	(21.9%)
	III	0	
	IV	12	(16.4%)

* NF – non-functional tumor.

Table 2. Demographic and clinicopathological characteristics of patients with non-P-NETs.

Demographic and pathological features		Number n=92	
Gender	Male	41	(44.6%)
Age (years) at diagnosis	Median (range)	45	(20–78)
Subtype	Malignant lesion	60	(65.2%)
	Benignant lesion	32	(34.8%)
Surgery or not	Resection	82	(89.1%)
	Non-resection	10	(10.9%)

Figure 4 shows the diagnostic accuracy of CgA in P-NETs. An ROC curve showed that a CgA concentration of 77.8 ng/ml could differentiate patients with P-NETs from those with non-P-NETS, with a sensitivity of 61.6%, a specificity of 76.1%, and an AUC of 0.741 (Figure 4A). A CgA concentration of 61.42 ng/ml could differentiate patients with insulinomas from those with non-P-NETS, with a sensitivity of 100%, a specificity of 40.2%, and an AUC of 0.632 (Figure 4B). In addition, a CgA concentration of 77.8 ng/ml could differentiate patients with non-insulinoma P-NETs from those with non-P-NETS, with a sensitivity of 96.7%, a specificity of 76.1%, and an AUC of 0.897 (Figure 4C).

Potential factors influencing CgA level in P-NET group

When patients with P-NETs were divided into 2 groups based on the CgA cut-off of 77.8 ng/ml, univariate analysis showed that higher serum CgA level was closely related to tumor subtype and the presence of liver metastases (Table 3). In the present study, 86.7% (26/30) of the patients with non-insulinoma had high CgA, compared with 44.2% (19/43) of the patients with insulinoma had CgA ($p<0.01$). In addition, 91.6% (11/12) of the patients with liver metastases had serum CgA levels over the cut-off value, compared with 55.7% (34/61) of the patients without liver metastasis ($p=0.023$). When all potentially

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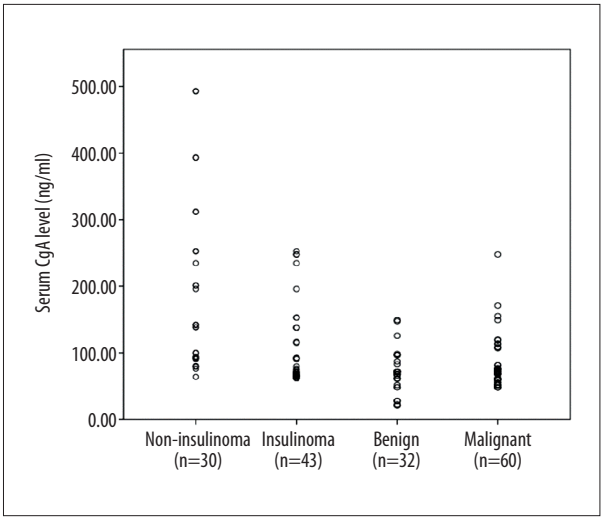

Figure 3. Serum CgA concentrations of subgroups of patients in the P-NET and non-P-NET groups.

significant factors with P values <0.2 were included in multivariate logistic regression analysis, non-insulinoma and the presence of liver metastases were found to be independently associated with elevated serum CgA level (both P<0.001).

Discussion

Despite its rarity and heterogeneous nature, the incidence and prevalence of P-NETs have increased during the past decades. Because early diagnosis can improve patient prognosis [29,34], diagnostic methods are required for P-NETs. Few studies, however, have assessed serum biomarkers diagnostic for P-NETs. Studies in western countries have shown that serum CgA concentration is a diagnostic biomarker for NETs [35–37]. To date, serum CgA levels have not been routinely measured or applied to manage patients with NETs in China, and no serum biomarker has been shown diagnostic for P-NETs. The present study therefore assessed whether serum CgA concentration is a reliable biomarker for P-NETs in Chinese patients.

Serum CgA measurements can contribute to the differential diagnosis of P-NETs and other pancreatic diseases. Although elevated serum CgA levels have been observed in patients with pancreatic cancer [21,38], the present study found that serum CgA levels were significantly higher in patients with P-NETs than in patients with malignant pancreatic lesions, including adenocarcinomas and intraductal papillary mucinous neoplasms, and patients with other benign pancreatic lesions. Serum CgA levels did not differ significantly, however, between patients with malignant and benign pancreatic lesions, indicating that serum CgA concentration could distinguish P-NETs from the other pancreatic lesions. Assessment of the serum CgA cut-off value distinguishing P-NETs and other pancreatic lesions showed that a concentration of 77.8 ng/ml was an appropriate cut-off, with a sensitivity of 61.6% and a specificity of 76.1%. These findings were consistent with the results of a study in Japan, which found that a cut-off of 78.7 ng/ml had a sensitivity of 53.6% and a specificity of 78.6% [39].

Serum concentrations of CgA are not elevated in patients with insulinomas, the most common type of functional P-NET [40–42]. The present study also found that CgA levels did not differ significantly between patients with insulinomas and those with non-P-NET pancreatic lesions. In contrast, serum

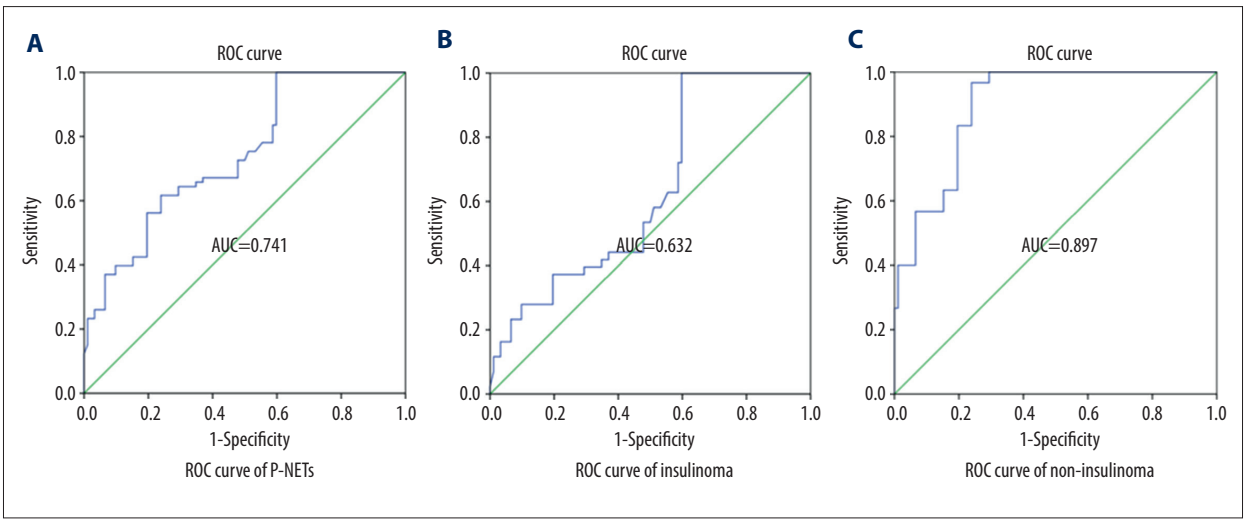

Figure 4. Diagnostic accuracy of CgA in patients with P-NETs. (**A**) ROC curve of CgA concentrations in patients with P-NETs (n=73) and non-P-NETs (n=92). (**B**) ROC curve of CgA concentrations in patients with insulinoma (n=43) and non-P-NETs (n=92). (**C**) ROC curve of CgA concentrations in patients with non-insulinoma P-NETs and (n=30) and non-P-NETs (n=92). AUC – area under the curve.

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Table 3. Clinicopathological factors and serum CgA concentrations in patients with P-NETs.

Factor	Total (n=73)	<Cut-off (n=28)	≥Cut-off (n=45)	*P*-value	Logistic χ^2	*P*-value
Age (%)						
≥49(years)	37	14 (37.8%)	23 (62.2%)	1		
<49(years)	36	14 (38.9%)	22 (61.1%)			
Sex (%)						
Male	29	13 (44.8%)	16 (55.2%)	0.462		
Female	44	15 (34.1%)	29 (65.9%)			
P-NETs subtype				<0.01**	18.4	<0.001*
Insulinoma	43	24 (55.8%)	19 (44.2%)			
Non-insulinoma	30	4 (13.3%)	26 (86.7%)			
Histological grade (%)				0.143	0.015	0.902
G1–G2	65	27 (41.5%)	38 (58.5%)			
G3	8	1 (12.5%)	7 (87.5%)			
Liver metastasis (%)				0.023*	14.6	<0.001*
Yes	12	1 (8.3%)	11 (91.6%)			
No	61	27 (44.3%)	34 (55.7%)			

* $P<0.05$. calculated using χ^2 test or Fisher's exact test.

CgA levels were significantly higher in patients with non-insulinoma P-NETs than in patients with insulinoma, suggesting that serum CgA may be a sensitive marker for differentiating non-insulinoma P-NETs from other pancreatic lesions. Interestingly, however, positive expression of CgA has been observed in insulinoma tissues [43], despite low serum concentrations. The potential mechanism underlying differences in CgA concentrations should be further explored to better clarify the relationship between CgA and P-NETs.

Elevated serum CgA levels were found to be strongly associated with greater tumor burden and metastasis of NETs [26,27,44]. In the present study, multivariate analysis indicated that the presence of liver metastases was likely associated with elevated serum CgA. These findings suggest that serum CgA level may be used to estimate tumor burden of P-NETs in Chinese patients. Additional studies are needed to confirm whether serum CgA could predict prognosis of Chinese patients with P-NETs. Although histological grade did not affect serum CgA level, 7 of the 8 patients with G3 P-NETs had high serum CgA levels. Subgroup analysis could not be performed due to the limited number of patients.

This study has several limitations. First, due to the rarity of P-NET, only 73 patients were included, which limited the level of evidence. Second, all of the enrolled patients were inpatients at a single center, resulting in possible selection bias. Additional studies in larger populations are required to determine the relationships between serum CgA and disease stage. In addition, the ability of CgA concentration to predict treatment outcomes and prognosis in Chinese patients with P-NETs remains to be determined.

Conclusions

In conclusion, serum CgA is a valuable diagnostic biomarker for Chinese patients with P-NETs, especially those with non-insulinoma P-NETs. Elevated serum CgA may be associated with liver metastases.

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